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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,443	02/05/2002	Bruce Spiegelman	DFN-038	3678

959 7590 01/26/2004

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EXAMINER	
FREDMAN, JEFFREY NORMAN	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 01/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,443	SPIEGELMAN ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-77* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 44-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XV, claim 37 in the paper filed November 21, 2003 is acknowledged. The traversal is on the ground(s) that Group XV should be reformed to include claims 34-43 and 75 and that other Groups should also be reformed. Since Applicant has indicated that they elect the Group which would comprise claim 37, it is not necessary to address the issue of whether other groups should be reformed. However, the current examiner agrees with Applicant that the elected Group should contain claims 34-43. Claim 75 is drawn to a reach-through product claim and is distinct as capable of being made by other methods (such as chemical synthesis) and burdensome to search since the search for products, which might include the well known drug Metformin, would be entirely different than the search for the method. So Applicant's arguments are accepted in part and claims 34-43 will be examined. Claims 1-33 and 44-77 are withdrawn from prosecution as drawn to non-elected groups.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 34-36 and 38-43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for direct measurement of PGC-1

expression as in claim 37, does not reasonably provide enablement for the use of surrogates such as glucose output or expression of one of phosphoenolpyruvate carboxykinase, glucose-6-phosphate or fructose 1,6 bisphosphatase as in claims 38-41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claims 38-41 are drawn to a method of screening for a compound that modulates gluconeogenesis where the measurement of the modulation of the expression of PGC-1 is the determining factor regarding gluoconeogenesis and in which that expression is not directly measured, but is measured by a surrogate such as glucose output or expression of one of phosphoenolpyruvate carboxykinase, glucose-6-phosphate or fructose 1,6 bisphosphatase. The invention is in an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of screening for a compound that modulates gluconeogenesis by analyzing PGC-1 expression not just by measurement of the mRNA of the PGC-1 gene but also by use of surrogates such as glucose output or expression of one of phosphoenolpyruvate carboxykinase, glucose-6-phosphate or fructose 1,6 bisphosphatase. The method broadly encompasses the use of the method in any cell type, in a tumor, in any type of mammalian patient. Further, the cells undergoing the test may be subject to any of a variety of different conditions depending upon the particular patient studied, with insulin dependent patients, for example receiving daily doses of a compound which significantly alters cellular metabolism while cancer patients may be receiving chemotherapeutic treatments, pain medicine for surgery, corticosteroids to reduce trauma associated with surgery which themselves significantly impact cellular metabolism or any of a number of other complicating factors which impact the expression of components of PGC-1. For example, PGC-1 is directly tied to thermoregulation (see Boss et al, Biochem. Biophys. Res. Comm. (1999) 261:870-876 who teaches that cold can alter PGC-1 expression as shown in figure 1). So, the claims encompass the use of any surrogate for analysis of PGC-1 including those specifically identified in claims 40 and 41.

Quantity of Experimentation

The quantity of experimentation in this area is large since there is significant variability in the expression of PGC-1 depending upon the cell type, cell environment as discussed above regarding temperature, insulin treatment, chemotherapeutic or other treatments which is an inventive, unpredictable and difficult undertaking in itself, and

efficacy of other elements as true surrogates for PGC-1 expression linked with gluconeogenesis would need to be demonstrated in a variety of different cell type models. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

The unpredictability of the art and the state of the prior art

The art teaches that many factors may induce PGC-1 expression and that many factors which are responsive to PGC-1 may be induced by other signals. For an example of a factor which can induce PGC-1 expression, Boss et al, Biochem. Biophys. Res. Comm. (1999) 261:870-876 teaches that cold can alter PGC-1 expression as shown in figure 1.

With regard to the use of secondary measurements to determine PGC-1 expression, it is entirely unpredictable whether, for example, a compound which modulates glucose output will perform this modulation via a PGC-1 pathway and induce or repress PGC-1, or operate by a different pathway. Barthel et al (Am. J. Physiol. Endocrinol. Metab. (2003) 285:e685-692) notes "Analogous to multiple braking systems in cars or motorbikes, the redundancy in the regulation of hepatic glucose production emphasizes the critical importance of this process in the glucose homeostasis of the organism (see page e689, column 1)." Thus, Barthel expressly teaches that multiple different pathways may affect glucose output, not all of which include PGC-1. Consequently, measurement of glucose output may have no relevance for the PGC-1 expression status of cells induced with some compounds. Barthel expressly shows this by stating "In addition to PGC-1, insulin might also target transcriptional coactivator proteins of the p300/CREBP family, which play a central role in the integration of cellular

signaling processes (see page e689, column 1)." Thus, compounds which interact with p300 may affect glucose output without altering the level of PGC-1, for example. Barthel provides numerous other pathways which may affect glucose output without a direct effect on PGC-1 expression levels (see pages e686-e688).

Further, with regard to the three specific genes listed, each of these genes is activated by proteins other than PGC-1. For example, Crawford et al (J. Biol. Chem. (1998) 273(22):13387-13390) teaches that nuclear factor I binds to the promoter of the phosphoenolpyruvate carboxykinase gene, and thereby modulates expression of this gene. So compounds which induced NF-1, but had no effect on PGC-1, would cause altered expression of the phosphoenolpyruvate carboxykinase gene but would have no impact on the modulation of PGC-1. Similarly, Ayala et al (Diabetes (1999) 48:1885-1889) teaches that the human glucose-6-phosphatase gene is activated by NF-1 or by FKHR acting based upon insulin stimulation (see abstract). Here again, compounds which induce FKHR or NF-1 may directly impact the expression of the human glucose-6-phosphatase gene without any concomitant effect on the expression of PGC-1. Lastly, Herzog et al (Biochem J. (2000) 351:385-392) teaches that the fructose 1,6-bisphosphatase gene is regulated by a number of elements including NF-kB, SP1 and USF1/USF2 (see abstract). So in the case of the fructose 1,6-bisphosphatase gene, compounds which induce or repress NK-kB, SP1 or USF1/USF2 may directly impact the expression of the gene without any concomitant effect on the expression of PGC-1

Therefore, the prior art demonstrates that there are multiple pathways for the expression and activation of each of the cited reporter elements in claims 38-41 and that these reporter elements will not necessarily demonstrate expression of PGC-1, but rather will simply show some effect. It would require direct measurement of PGC-1

expression, as in claim 37, to demonstrate that the compound is, in fact, altering the expression or activity of PGC-1.

Thus, the ordinary practitioner would not expect these reporters to function as a successful reporter elements of PGC-1 expression in view of the teachings in the art that there are multiple systems which impact expression and which are involved in the regulation of glucose production in the hepatic system.

Working Examples

The specification has a working example as per the enabled scope in which PGC-1 expression is directly detected.

Guidance in the Specification.

The specification, while suggesting the use of surrogate reporter systems, does not provide sufficient basis to verify whether these surrogates will function to show a change in the expression or activity of PGC-1. While the specification, for example, shows an association between glucose output and PGC-1 expression (see example 3 beginning on page 77), this showing that PGC-1 is capable of impacting glucose output does not show that PGC-1 expression is necessary and essential for a change in glucose output. As Barthel indicates above, many pathways may effect glucose output and the specification does not provide sufficient guidance to determine whether when a cell is contacted with a compound which, for example, induces increased glucose output, that increased glucose output is correlated with increased PGC-1 expression. While sometimes, for some unpredictable set of compounds, PGC-1 will be induced, the specification provides no guidance on how to determine, based solely upon a measurement of glucose output, or expression of one of phosphoenolpyruvate

carboxykinase, glucose-6-phosphate or fructose 1,6 bisphosphatase, whether PGC-1 was or was not modulated in expression or activity.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching that each of the reporters may be activated by non-PGC-1 modes (see Barthel, Ayala, Crawford and Herzog above) supports a finding of undue experimentation. Further, the specification provides one with no written description or guidance that leads one to a reliable method determining when these reporters, or other unnamed and undisclosed reporters, would demonstrate PGC-1 modulation of expression or activity as discussed above. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is concluded that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 34-35 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Wu et al (Cell (1999) 98:115-124).

Wu teaches a method comprising:

a) contacting a cell with a compound (see page 117, figure 2, where myoblasts were treated with 100 nM T3)

b) determining whether PGC-1 expression was modulated (see page 117, figure 2, panel A, where PGC-1 mRNA expression is shown).

With regard to claim 35, Wu teaches that treatment with a compound induces PGC-1 activity (see page 117, columns 1 and 2).

With regard to claim 37, Wu teaches measurement of PGC-1 by northern blotting (see page 117, figure 2).

6. Claims 34-36 and 42-43 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al (Am. J. Physiol. Endocrinol. Metab. (Aug 2000) 279:E433-446).

Yu teaches a method comprising:

a) contacting a hepatocyte cell with a compound, here LPS (see page e436, column 2, where mice were treated with LPS)

b) determining whether PGC-1 expression was modulated (see page e437, figure 3, where PGC-1 mRNA is measured).

With regard to claim 35, Yu teaches that treatment with a compound induces PGC-1 activity in skeletal muscle cells (see page e437, figure 3).

With regard to claim 36, Yu teaches that treatment with a compound decreases PGC-1 activity in liver cells (see page e437, figure 3).

With regard to claims 42-43, Yu teaches the use of hepatocytes from whole liver, which inherently comprises primary hepatocytes (see page e436, column 2).

7. Claims 34-37 and 41-43 are rejected under 35 U.S.C. 102(e) as being anticipated by Spiegelman et al (U.S. Patent 6,166,192)

Spiegelman teaches a method (also see column 36, lines 47-67) comprising:

a) contacting a hepatocyte (liver cell) with a compound, here insulin (see column 15, lines 1-31)

b) determining whether PGC-1 expression was modulated (see column 15, lines 1-10, where glucose output is used as a surrogate for PGC-1 expression).

With regard to claims 35 and 36, Spiegelman teaches that treatment with a compound may increase or decrease PGC-1 activity (see column 15, lines 8-10).

With regard to claim 37, Speigelman teaches the use of northern blotting (see column 40, line 53).

With regard to claim 41, Spiegelman expressly teaches measurement of glucose output (see column 15, lines 1-10).

With regard to claims 42-43, Spiegelman teaches the use of liver cells, which inherently comprises primary hepatocytes (see column 15, lines 1-10).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claim 34-37 and 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al (Am. J. Physiol. Endocrinol. Metab. (Aug 2000) 279:E433-446) in view of Wu et al (Cell (1999) 98:115-124).

Yu teaches a method comprising:

a) contacting a hepatocyte cell with a compound, here LPS (see page e436, column 2, where mice were treated with LPS)

b) determining whether PGC-1 expression was modulated (see page e437, figure 3, where PGC-1 mRNA is measured).

With regard to claim 35, Yu teaches that treatment with a compound induces PGC-1 activity in skeletal muscle cells (see page e437, figure 3).

With regard to claim 36, Yu teaches that treatment with a compound decreases PGC-1 activity in liver cells (see page e437, figure 3).

With regard to claims 42-43, Yu teaches the use of hepatocytes from whole liver, which inherently comprises primary hepatocytes (see page e436, column 2).

Yu does not teach measurement of mRNA levels by northern blotting.

Wu teaches measurement of mRNA levels by northern blotting (see page 117, figure 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to since northern blotting is a known equivalent technique for measurement of mRNA levels as shown by Wu and since MPEP 2144.06 notes " Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to

render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)." Here, the PCR method of Yu and the northern blot of Wu are known equivalents and it would have been obvious to substitute one method for the other.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jeffrey Fredman
Primary Examiner
Art Unit 1634